REMARKS

1. General Matters

All multiple dependency has been eliminated. Hence, all claims should be examined on the merits.

2. Definiteness Issues

2.1. The Examiner questions whether there is a conflict between the common meaning of "cell" (in "a RS virus related biological cell" in claim 1) and claim 4 (reciting that the "cell...is a virus particle").

Claim 1 has been amended to recite binding a cell or "biological particle". Claim 4 has been amended to refer to the latter.

2.2. By "RS virus related cell", applicant meant an RS virus infected cell. This is evident from, e.g., page 1, lines 5-9 and page 9, lines 4-10.

2.3. In the preamble to claim 1, "2000 per microliter" means 2000 cells per microliter sample specimen as described at page 11, line 32. Claim 1 has been amended to include the clarification. Claim 1 does not refer to any upper limit on the total volume assayed, since it is the concentration of cells/particles per sample volume that is of interest.

2.4. The Examiner questions whether the targeting species is linked to the solid support via the polymeric carrier.

In claim 1, element (i) is a solid support. Element (ii) are targeting species bound to that support. Element (iii) is a conjugate of a polymeric carrier molecule to both (a) at least one targeting species and (b) at least one labeling species. The claim does not require that the targeting species attached to the carrier in element (iii) be one of the targeting species of element (ii). Likewise, it is not required that the targeting species be coupled to the solid support via that carrier.

Nor is it required that the targeting species of element (ii) be labeled, see page 28, lines 13-14.

2.5. The antecedent basis problem in claim 1, parts (ii)

and (iv) is resolved bY deleting "said".

It is noted that "predetermined" does not mean already detected, but rather that the practitioner has chosen which RS virus to attempt to detect. This can, of course, affect the choice of targeting species.

2.6. We have followed the Examiner's suggestion to recite "binding" rather than "detecting".

2.7. With respect to claim 2, the Examiner is correct in asserting that the intent is to require a conjugation product made by process of linking the moieties together via reaction of functional groups, and claim 2 has been amended to reflect this.

3. Prior Art Issues

Claims 1-6 and 11-15 stand rejected as obvious over Wang (US 4,663,277) optionally further in view of either Burton et al. (US 5,762,905) or Langedijk (US 6,077,511). Claims 16-17 are rejected as obvious over the above art in view of Molday (US 4,452,773). Claims 1,2, 4-6, 14, 16 and 18 stand rejected as obvious over Wang et al or Burton et al or Langedijk et al., further in view of Cihme et al. (US 5,543,332). These rejections are respectfully traversed.

Before analyzing the rejections, we wish to observe that claim 1 has been amended to include language to the various zones of the kit. The basis for this amendment is found at pages 27-28, lines 39-6, in example 1 as well as Figure 1. By the amendments of claim 1 it has been clarified that the present invention relates to a kit wherein different zones being in liquid contact or fluid communication with each other when in use may be used for applying the sample and detecting bound conjugates, respectively. Such a kit may for example be a lateral flow device as discussed at page 1, line 27 and page 21,lines 33-35. One of the advantages of using two different zones for application and detection, respectively, is that at least one washing step may be avoided. After having formed complexes of the cells or particles bound to the conjugates in the application

zone the complexes are flown to the detection zone wherein only complexes being bound to the targeting species being bound to the solid support in the detection zone are maintained in the detection zone and conjugates not being part of complexes are flown away from the zone by the flow forces. The flow forces may be any suitable flow forces, such as capillary forces as in a lateral flow device, or active flow forces as in a micro system.

Wang (US 4,663,277) discloses an immunoassay method in which an extended solid phase coated with antiviral antibody is employed to bind and remove virions from a specimen by forming an immuno-complex with antigens of said virions, a mobile solid phase comprising a dispersion of microspheres coated with the antiviral antibody is used to bind the microspheres to the antigens associated with the immunocomplex, and the presence of bound microspheres is detected.

The extended solid phase in Wang may, for example, be a dipstick, wherein the end of the dipstick is coated with antiviral antibodies. The dipstick may then be inserted into the specimen to be tested, vide col 5, lines 36-44, washed to remove unbound specimen, inserted into microsphere dispersion, washed to remove unbound microspheres and then subjected to detection. Accordingly, the extended solid phase is first presented to the specimen and afterwards presented to the microspheres and subjected to at least two washing steps.

In Wang, there is no disclosure of a dipstick or the like wherein the microspheres are presented to the specimen in one zone and afterwards in liquid contact transported to a detection zone for being indirectly bound to the extended solid phase.

Burton (US 5,762,905) et al. disclose human monoclonal antibodies and fragments thereof which bind and neutralize RSV antigenic subgroups A and B. The reference discuss that the antibodies may be used for diagnostic methods, however, no specific methods are described.

Langedijk (US 6,077,511) discloses an antigenic substance or precursor thereof comprising a peptide part derived from an

amino acid sequence located between two mucin-like regions of a protein G of a respiratory syncytial virus. Use of antigenic substance or precursor thereof for prophylaxis of RSV infections, in assays and testkits for detecting or identifying RSV types.

By combining Wang and Burton or Langedijk the person skilled in the art may be taught how to use the dipstick of Wang with antibodies directed to RS virus. However, the person skilled in the art is not taught the invention as claimed by the present claim 1, wherein different zones being in liquid contact may be used for applying the sample and detecting bound conjugates, respectively.

Accordingly, the invention as claimed by amended claim 1 is non-obvious in view of Wang further in view of Burton or Langedijk.

Molday (US 4,452,773) discloses colloidal sized particles composed of magnetic iron oxide coated with a polysaccharide, preferably dextran, or a derivative thereof having pendant functional groups. The particles have a magnetic moment, are electron dense, and are stable and non-aggregating under physiological conditions. They can be covalently bonded to antibodies, enzymes and other biological molecules and used to label and separate cells, cellular membranes and other biological particles and molecules by means of a magnetic field, however no specific assay system is disclosed in the reference.

Even by combining Wang and Burton or Langedijk and Molday, the person skilled in the art is not taught the invention as claimed by the present claim 1, wherein different zones being in liquid contact with each other may be used for applying the sample and detecting bound conjugates, respectively.

Lihme et al. (US 5,543,332) disclose water soluble reagents comprising a water soluble polymeric carrier molecule having attached thereto more than one connecting moiety wherein the connecting moiety is attached to a reactive functional group on the polymeric carrier molecule. The connecting moiety may act as coupler to a labeling species, a marking species and targeting

species. The reference describes the use of the water soluble reagents in ELISA procedures and in Dot Blot immunoblotting.

There is no disclosure of the use of the water soluble reagents in a dipstick or the like device, in particular no disclosure of the possibility of having the water soluble reagents flowing from an application zone to a detection zone in an assay kit.

Furthermore, there is no hint in Lihme et al. that the water soluble reagents may be used in a dipstick or the like, since the only applications in Lihme et al. is ELISA and Dot Blot. It is pure hindsight to state that it was obvious to substitute the microspheres of Wang with the water soluble reagents of Lihme et al.

In particular even by combining Wang and Burton or Langedijk and Lihme the person skilled in the art is not taught the invention as claimed by the present claim 1, wherein different zones being in liquid contact with each other may be used for applying the sample and detecting bound conjugates, respectively.

Accordingly, the invention as claimed by amended claim 1 is non-obvious in view of Wang further in view of Burton or Langedijk further in view of Lihme et al.

Since claim 1 is thus novel and non-obvious, the dependent claim 2-23 are also novel and non-obvious.

Independent claims 24, 42 and 43 have been amended to include the claim language of claim 1. The argumentation for novelty and non-obviousness corresponds to the above for claim 1.

Previous claim 44 has been deleted without prejudice.

Singh et al (US 6,083,708) describes compositions comprising dendrimers to which a first polypeptide is controllably coupled. Such polypeptide-dendrimer compositions are effective for controllably coupling a second polypeptide to the dendrimer. Such compositions are useful as indicators in specific binding assays, e.g., immunoassays. Singh *et al.* is not relevant for the invention as claimed in present claim 1.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 1-4, 7, 10-21, 24, 28-34, 36-39, and 41-44 have been amended as follows:

1. (amended). A kit for directly detecting a RS virus related biological cell or biological particle present in a sample in an amount of less than about 2000 cells or particles per microlitre (10^{-6} litre), said kit comprising

i) a solid support, and

ii) a plurality of a first targeting species bound to the solid support, said targeting species being capable of directly ~~detecting said~~binding a predetermined RS virus related biological cell or biological particle when it is present in a sample that is brought into contact with the solid support, and

iii) a conjugate comprising a polymeric carrier molecule bound to

~~iv)~~a) at least one first and/or second targeting species capable of directly ~~detecting said~~binding a predetermined RS virus related biological cell or biological particle when it is present in a sample that is brought into contact with the solid support, and

~~v)~~b) at least one labelling ~~species.~~species,

iv) an application zone for applying the sample comprising a RS virus related biological cell or biological particle, said zone comprising at least one conjugate, said conjugate being movable, and said application zone being in liquid contact with

v) a detection zone for detecting the presence, amount or concentration of said at least one conjugate, said zone further comprising the plurality of a first targeting species bound to the solid support, and optionally

vi) a positive control zone generating a positive control confirming the transfer of at least part of said sample from said application zone to said detection zone.

2. (amended). Kit according to claim 1, wherein the conjugate comprises

i) a polymeric carrier ~~molecule comprising a plurality of at least one reactive, functional group~~,

~~iii)~~ii) at least one connecting moiety attached to the ~~at least one reactive, functional group,~~polymeric carrier molecule,

~~iii)~~

iii) at least one molecular species selected from the group of molecular species consisting of targeting species and labelling species, wherein each of the molecular species~~comprises at least one functional group that is~~~~reactive with~~ covalently attached to at least one connecting moiety attached to the ~~reagent,~~polymeric carrier molecule,

~~iv) wherein the conjugate comprises at least one molecular species covalently attached thereto via a connecting moiety.~~

~~iv)~~

~~1.~~3. Kit according to claim 2, wherein the polymeric carrier molecule comprises ~~reactive, functional groups~~connecting moieties in an amount of from about 5 to about 5,000 ~~□moles~~μmoles per gram of polymeric carrier.

4. (amended). Kit according to ~~any of the preceding claims,~~claim 1, wherein the RS virus related biological ~~cell~~particle capable of being directly ~~detected~~bound by a targeting species is a virus particle.

5. (amended). Kit according to claim 4, wherein the virus capable of being directly detected by a targeting species belongs to the genus paramyxoviridae.

6. (amended). Kit according to claim 5, wherein the virus is respiratory syncytial virus.

7. (amended). Kit according to ~~any of the preceding claims,~~claim 1, wherein the targeting species is selected from the group of species consisting of antigens; haptens; monoclonal and polyclonal antibodies; gene probes; natural and synthetic oligo- and polynucleotides; natural and synthetic mono-, oligo- and polysaccharides; lectins; avidin and streptavidin; biotin; growth factors; hormones; receptor molecules; protein A; and protein G.

8. (amended). Kit according to claim 7, wherein the targetting species is selected from monoclonal and polyclonal antibodies.

9. (amended). Kit according to claim 8, wherein the targetting species is an antibody recognising a nucleoprotein of RS virus or a glycoprotein of RS virus.

10. (amended). Kit according to ~~any of the preceding claims,~~claim 1, wherein the labelling species is selected from the group of species consisting of proteins; enzymes; toxins; drugs; dyes; fluorescent, luminescent, phosphorescent and other light-emitting substances cells; metal-chelating substances; substances labelled with a radioactive isotope; and substances labelled with a heavy atom.

11. (amended). Kit according to [any of claims 1 and 2] claim 1, wherein the labelling species is selected from the group of species consisting of ferritin, phycoerythrins, phycocyanins, phycobilins, horseradish peroxidase, alkaline phosphatase, glucose oxidases, galactosidases, ureases, iminodiacetic acid, ethylenediaminetetraacetic acid, diethylenetriaminepentaacetic acid, and desferrioxamine B.

12. (amended). Kit according to ~~any of~~ claim~~s 1 and~~ 2, wherein the first and second targeting species are identical.

13. (amended). Kit according to ~~any of~~ claim~~s 1 and~~ 2, wherein the first and second targeting species are non-identical.

14. (amended). Kit according to ~~any of claims 1 and~~claim 2, wherein the polymeric carrier is selected from the group of polymers consisting of natural and synthetic

polysaccharides; homopoly amino acids; natural and synthetic polypeptides and proteins; and synthetic polymers having nucleophilic functional groups.

15. (amended). Kit according to ~~any of~~ claim~~s 1 and~~ 2, wherein the polymeric carrier is selected from the group of polymers consisting of polyvinyl alcohols, polyallyl alcohols, polyethylene glycols and substituted polyacrylates.

16. (amended). Kit according to ~~any of claims 1 and~~claim 2, wherein the polymeric carrier is selected from the group consisting of dextrans, carboxymethyl-dextrans, starches, hydroxyethyl-starches, hydroxypropyl-starches, glycogen, agarose derivatives, cellulose derivatives and natural gums.

17. (amended). Kit according to claim ~~11,~~16, wherein the polymeric carrier is a dextran.

18. (amended). Kit according to ~~any of claims 1 and~~claim 2, wherein the polymeric carrier is selected from the group consisting of hydroxyethyl-celluloses and hydroxypropyl-celluloses.

19. (amended). Kit according to ~~any of the preceding claims,~~ claim 1, said kit being a dip-stick.

20. (amended). Kit according to ~~any of the preceding claims,~~ claim 1, said kit being adapted for a microsystem.

21. (amended). Kit according to ~~any of claims 1 to 20,~~ claim 1, further comprising means for detecting at least one inflammatory indicator.

22. (amended). Kit according to claim 21, wherein the at least one inflammatory indicator is a cytokine.

23. (amended). Kit according to claim 22, comprising means for detecting at least 3 different cytokines.

24. (amended). Method of detecting a~~RS virus related~~ predetermined RS virus related biological cell or biological particle present in a sample, said method comprising the steps of

~~i)contacting the sample with the kit of any of claims 1 to 24, and~~

~~ii)detecting a targeting species capable of targeting the predetermined RS virus related biological cell,~~

~~wherein the detection of the targeting species is indicative of the presence of the RS virus related biological cell in the sample.~~

i) ~~contacting the sample with a~~ providing a kit for directly detecting a RS virus related biological cell or biological particle present in a sample in an amount of less than about 2000 cells or biological particles per microlitre (10^{-6} litre), said kit comprising

A) a solid support, and

~~b)~~B) a plurality of a first targeting species bound to the solid support, said targeting species being capable of directly ~~detecting said~~binding a predetermined RS virus related biological cell or biological particle when it is present in a sample that is brought into contact with the solid support, and

~~c)~~C) a conjugate comprising a polymeric carrier molecule bound to

~~to i)~~

a) at least one first and/or second targeting species capable of directly ~~detecting said~~binding a predetermined RS virus related biological cell or biological particle when it is present in a sample that is brought into contact with the solid support, and

~~and ii)~~

b) at least one labelling species,

D) an application zone for applying the sample comprising a RS virus related biological cell or biological particle, said zone comprising at least one conjugate, said conjugate being movable, and said application zone being in liquid contact with

E) a detection zone for detecting the presence, amount or concentration of said at least one conjugate, said zone further comprising the plurality of a first targetting species bound to the solid support, and optionally

F) a positive control zone generating a positive control confirming the transfer of at least part of said sample from said application zone to said detection zone.

ii) contacting the sample with the kit of step i), and

~~ii)~~iii) detecting a ~~targeting species~~conjugate capable of ~~targeting~~binding the predetermined ~~inflammatory indicator,~~RS virus related biological cell or biological particle,

wherein the detection of the ~~targeting species~~conjugate is indicative of the presence of the ~~predetermined inflammatoryindicator~~RS virus related biological cell or biological particle in the sample.

25. (amended). Method according to claim 24, wherein the sample is a body fluid sample.

26. (amended). Method according to claim 24, said kit further comprising means for detecting at least one predetermined inflammatory indicator.

27. (amended). Method according to claim 26, wherein the inflammatory indicator is present in the sample in an amount of less than about 100 nanograms (100×10^{-9} grams) per millilitre (10^{-3} litre).

28. (amended). Method according to ~~any of claims 24-27,~~claim 24, wherein the polymeric carrier molecule comprises i) a plurality of at least one~~reactive,~~

~~functional group, ii) at least one~~ connecting moiety attached to ~~the at least one reactive, functional~~polymeric carrier group, and iii) at least one molecular species selected from the group of molecular species consisting of targeting species and labelling species, wherein each of the molecular species ~~comprises at least one functional group that is reactive with~~is attached to at least one connecting moiety attached to the ~~reagent, and wherein the conjugate comprises at least one molecular species covalently attached thereto via a connecting moiety.~~polymeric carrier molecule.

29. (amended). Method according to any of claim~~s 24-28,~~ wherein the targeting species is selected from the group of species consisting of antigens; haptens; monoclonal and polyclonal antibodies; gene probes; natural and synthetic oligo- and polynucleotides; natural and synthetic mono-, oligo- and polysaccharides; lectins; avidin and streptavidin; biotin; growth factors; hormones; receptor molecules; protein A; and protein G.

30. (amended). Method according to ~~any of~~ claim~~s 24-29,~~ wherein the labelling species is selected from the group of species consisting of proteins; enzymes; toxins; drugs; dyes; fluorescent, luminescent, phosphorescent and other light-emitting substances; metal-chelating substances; substances labelled with a radioactive isotope; and substances labelled with a heavy atom.

31. (amended). Method according to ~~any of~~ claim~~s 24-30,~~ wherein the labelling species is selected from the group of species consisting of ferritin, phycoerythrins, phycocyanins, phycobilins, horseradish peroxidase, alkaline phosphatase, glucose oxidases, galactosidases, ureases, iminodiacetic acid, ethylenediaminetetraacetic acid, diethylenetriaminepentaacetic acid, and desferrioxamine B.

32. (amended). Method according to ~~any of~~ claim~~s 24-31,~~ wherein the polymeric carrier is selected from the group of polymers consisting of natural and synthetic polysaccharides; homopoly amino acids; natural and synthetic polypeptides and proteins; and synthetic polymers having nucleophilic functional groups.

33. (amended). Method according to ~~any of~~ claim~~s 24-32,~~ wherein the polymeric carrier is selected from the group of polymers consisting of polyvinyl alcohols, polyallyl alcohols, polyethylene glycols and substituted polyacrylates.

34. (amended). Method according to ~~any of claims 24-33,~~ claim 24, wherein the polymeric carrier is selected from the group consisting of dextrans, carboxymethyl-dextrans, starches, hydroxyethyl-starches, hydroxypropyl-starches, glycogen, agarose derivatives, cellulose derivatives and natural gums.

35. (amended). Method according to claim 34, wherein the polymeric carrier is a dextran.

36. (amended). Method according to ~~any of claims 24-34~~claim 24 , wherein the polymeric carrier is selected from the group consisting of hydroxyethyl-celluloses and hydroxypropyl-celluloses.

37. (amended). Method according to ~~any of~~ claim~~s 24 to 36,~~26 wherein the predetermined inflammatory indicator is selected from the group consisting of agonists from the IL-1 system, preferably IL-1α, IL-1β, IL-1ra, autoantibodies against IL-1α, sIL1-RI and sIL1-RII.

38. (amended). Method according to ~~any of~~ claim~~s 24 to 37~~26, wherein the predetermined inflammatory indicator is selected from the group consisting of agonists from the TNFα system, preferably sTNFR p55 and p75.

39. (amended). Method according to ~~any of~~ claim~~s 24 to 38~~26, wherein the predetermined inflammatory indicator is selected from the group consisting of IL-6 and autoantibodies against IL-6.

40. (amended). Method according to claim 26, wherein the predetermined inflammatory indicator is selected from the group consisting of IL-12, sIL-4R, TNFβ (LT), INFγ, IL-4, and IL-10.

41. (amended). Method according to ~~any of claims 24 to 40,~~ claim 26, wherein the predetermined inflammatory indicator is selected from the group consisting of IL-2, RANTES, IL-8, sIL-2R, IL-18, IFNα, and eosinophil cationic protein.

42. (amended). A method for diagnosing a RS virus infectious condition in an individual, said method comprising the steps of

~~iii) detecting a predetermined RS virus related biological cell present in a body fluid sample according to any of claims 24 to 41, and~~

~~iv) diagnosing said infectious condition.~~

i) providing a kit for directly detecting a RS virus related biological cell or biological particle present in a sample in an amount of less than about 2000 cells or particles per microlitre (10^{-6} litre), said kit comprising

A) a solid support, and

B) a plurality of a first targeting species bound to the solid support, said targeting species being capable of directly binding a predetermined RS virus related biological cell or biological particle when it is present in a sample that is brought into contact with the solid support, and

C) a conjugate comprising a polymeric carrier molecule bound to

a) at least one first and/or second targeting species capable of directly binding a predetermined RS virus related biological cell or biological particle when it is present in a sample that is brought into contact with the solid support, and

b) at least one labelling species,

D) an application zone for applying the sample comprising a RS virus related biological cell or biological particle, said zone comprising at least

one conjugate, said conjugate being movable, and said application zone being in liquid contact with

E) a detection zone for detecting the presence, amount or concentration of said at least one conjugate, said zone further comprising the plurality of a first targetting species bound to the solid support, and optionally

F) a positive control zone generating a positive control confirming the transfer of at least part of said sample from said application zone to said detection zone.

ii) contacting the sample with the kit of step i), and

~~i)~~iii) detecting a conjugate capable of binding the predetermined RS virus related biological cell or biological particle, wherein the detection of the conjugate is indicative of the presence of the RS virus related biological cell or biological particle in the sample.

iii) diagnosing said infectious condition.

43. (amended). The method according to ~~any of claims 24 to 42,~~claim 42 comprising the steps of

~~ii)~~i) ~~detecting a predetermined RS virus related biological cell present in a body fluid sample according to any of claims 24 to 42,~~detecting a predetermined inflammatory indicator present in a body fluid detecting a predetermined inflammatory indicator present in a body fluid sample, and

ii) ~~detecting a predetermined inflammatory indicator present in a body fluid sample according to any of claims 26 to 42, and~~ detecting a predetermined inflammatory indicator present in a body fluid sample, and

iii) diagnosing said infectious condition.

Claim 44 has been cancelled.